

Original Article

Predicting Outcomes of Oral Food Challenges by Using the Allergen-specific IgE–Total IgE Ratio

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What is already known about this topic? Past studies focused on less persistent food allergens (ie, milk, egg, wheat). A lower ratio was significantly correlated with passing challenges but was not more accurate than allergen-specific IgE alone in predicting challenge outcome.

What does this article add to our knowledge? This article is the first to study more persistent food allergens (ie, peanut, tree nuts, shellfish, seeds). The specific IgE to total IgE ratio was significantly more accurate than allergen-specific IgE alone in predicting the outcome of challenges performed to confirm the development of tolerance.

How does this study impact current management guidelines? Specific IgE to total IgE ratios may be useful identifiers of patients likely to pass oral food challenge. With further research to determine optimal predictive cutoff points, our findings may change current clinical practice.

BACKGROUND: Although allergists typically use allergen-specific IgE (sIgE) levels or skin prick test wheal sizes to identify food allergens that may provoke IgE-mediated food-induced allergic reactions, both tests have high rates of false positivity and mislabel patients who are tolerant as allergic to the food allergen.

OBJECTIVE: To examine the accuracy of the ratio of sIgE to total IgE (“Ratio”) in predicting the outcome of challenges performed to confirm the development of tolerance.

METHODS: Medical records of children diagnosed with food allergy who participated in oral food challenge at an allergy outpatient clinic (2009-2013) were reviewed for IgE antifood serology and concomitant oral food challenge outcomes, which were analyzed for associations by using logistic regression models and receiver operator characteristics curves.

RESULTS: The Ratio for participants who failed their challenge was higher than the Ratio of those who passed their challenge (failed 1.48% vs passed 0.49%; $n = 195$). Receiver operator characteristic curves showed that the Ratio was significantly more accurate than sIgE alone in predicting challenge outcome (Ratio 0.69 vs sIgE alone 0.55; $P = .03$). These trends were mostly associated with more persistent food allergens, such as peanut, tree nuts, shellfish, and seeds (failed 2.18% vs passed 0.41%; $n = 93$) (Ratio 0.81 vs sIgE alone 0.54; $P < .01$).

CONCLUSION: Our findings suggest that the Ratio is more accurate than sIgE alone in predicting outcomes of challenges performed to confirm the development of tolerance to select food allergens, especially to peanut and tree nuts. The Ratio may be useful in identifying patients most likely to pass oral food challenge. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)

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The double-blind, placebo-controlled food challenge remains the criterion standard for determining food allergen tolerance.¹ Allergists typically use allergen specific IgE (sIgE) levels or skin prick test wheal sizes to identify food allergens that may provoke IgE-mediated food-induced allergic reactions. Although both tests have high sensitivity and high negative predictive values, their low specificity and poor positive predictive values may result in the misdiagnosis of food allergy.²⁻⁶ Such high rates of false positivity result in mislabeling some patients who are tolerant as allergic to the food allergen. Additional criteria to identify patients most likely to pass oral food challenge would be useful in clinical practice.

When considering that food allergy is often associated with other IgE-mediated atopic conditions, one should interpret sIgE levels differently in patients with high total IgE (tIgE) levels

Abbreviations used*AUC*- Area under the curve*OFC*- Oral food challenge*OR*- Odds ratio*Ratio*- Ratio of allergen-specific IgE to total IgE*ROC*- Receiver operator characteristic*sIgE*- Allergen-specific IgE*tIgE*- Total IgE

compared with those with low levels. Indeed, Mehl et al⁷ found a significant correlation between the patient's ratio of sIgE to tIgE and the outcome of food challenge in diagnosing newly suspected milk, egg, and wheat allergy. The objective of the current study was to examine the accuracy of the ratio of the sIgE to tIgE (the "Ratio") in predicting the outcome of challenges performed to confirm the development of tolerance to all common food allergens, including peanut and tree nuts.

METHODS

Medical records of children diagnosed with IgE-mediated food allergy who participated in oral food challenge at an allergy outpatient clinic (Chicago, Ill) were reviewed. Children were diagnosed by an allergist based on clinical history, as supported by significantly positive skin prick test wheal sizes and/or allergen sIgE levels. Development of tolerance of the food allergen was based on the outcome of oral food challenge. The institutional review board of Northwestern University (Chicago, Ill) approved the study protocol.

Patient selection

All charts that contained documentation of oral food challenge between June 2009 and May 2013 were reviewed. Chart reviews were conducted by a research assistant (C.H.L.) who collected the oral food challenge date and outcome, type of food challenged, sIgE and tIgE test date and results, comorbid food allergies, history of other atopic comorbidities, birth date, and sex. A board-certified allergist in the clinic (K.K.N.) reviewed any questions or concerns raised by the research assistant during data collection and validated a randomly selected 10% of charts in the final sample. No errors were found during the validation process.

Data were collected for 572 oral food challenges among 427 children. Oral food challenge was excluded if the tIgE level was absent, if the sIgE or tIgE levels were lower than the detection limit of the assay, if blood samples were drawn more than 200 days before challenge, or if sIgE and tIgE levels were calculated from separate blood samples. Furthermore, our analysis only included challenges to milk, egg, wheat, soy, peanut, tree nuts, shellfish, and seeds, and resulted in a final sample size of 195 oral food challenges among 161 children. The basic demographic characteristics associated with the original 572 challenges identified were similar to the characteristics associated with the final sample of 195 challenges.

IgE levels

Blood was collected by venipuncture before oral food challenge. Patient sera were analyzed for the level of tIgE and sIgE to the offending food allergen by using the ImmunoCAP auto-analyzer (ThermoFisher Scientific, Phadia Division, Kalamazoo, Mich). The analytical sensitivity or lower detection limit was <0.1 kU_A/L for the sIgE assay and <2 kU/L for the tIgE assay.

A 1 kU_A/L of sIgE has been shown to be equivalent to 1 kU/L of tIgE in the ImmunoCAP System.⁸

Oral food challenges

Open oral food challenges were performed with parental consent when the allergist assessed that the child may have developed tolerance to the food allergen. This assessment was individualized based on the timing and severity of the last allergic reaction, the degree of skin prick sensitization less than an 8-mm wheal cutoff, and sIgE values less than previously reported 90% positive predictive value cutoffs for common food allergens, treating sesame seed decision points similar to those for peanut.^{2-4,6,9} The parents of the children were asked to withhold antihistamine medications at least 5 days before challenge. Each patient was examined immediately before challenge to ensure good health and optimal control of concomitant allergic disease.

Foods were separated into 7 incrementally doubling doses, up to a final dose of half a serving size. The total cumulative quantity of food ingested was one complete serving size according to its nutrition facts label. Increasing doses were administered at 10- to 15-minute intervals over 2 hours. To proceed to the next dose, the child must remain asymptomatic without vital sign instability. Emergency medications and equipment necessary to manage anaphylaxis were readily available. Challenge was discontinued if clinical symptoms were observed or if the highest dose was achieved. Children were examined, and vital signs were measured one final time, 30 minutes after ingestion of the final dose. The day after the challenge, a member of the office staff called the patient's home to document any late-phase symptoms. The challenge was only documented as "passed" if the child had been reaction-free up to this point.

Statistical analysis

The Ratio was calculated by using the following formula: Ratio = (sIgE/tIgE) × 100.

For the purposes of this article, "more persistent food allergens" will refer to peanut, tree nuts, shellfish, and seeds as a group; "less persistent food allergens" will refer to milk, egg, wheat, and soy as a group. Multiple logistic regression models were estimated to assess statistical correlations between the outcome of oral food challenge and the Ratio. Each model was adjusted for clustering (ie, children with multiple challenges) and controlled for age at challenge. Performance characteristics (eg, sensitivity, specificity, positive predictive value, negative predictive value) of various potential decision points for the Ratio were calculated. Receiver operator characteristic curves were fitted, and the area under the curve was computed to compare the accuracy of the Ratio with sIgE alone in predicting the outcome of challenges performed to confirm the development of tolerance to the food allergen. All statistical analyses were performed by using Stata/SE 12.1 (Stata Corp LP, College Station, Tex). For all analyses, a *P* value of <.05 was considered statistically significant, unless a more stringent level of *P* < .01 was indicated.

RESULTS

Study population demographics

The age at the time of oral food challenge ranged from 11 months to 18 years (median, 4.0 years). The majority of the children were boys (57%), were allergic to multiple food allergens (76%), and had a history of other atopic comorbidities (86%). These histories of other atopic comorbidities included asthma (34%), eczema (68%), and allergic rhinitis (45%).

The pass rate for all oral food challenges was 81%. Oral food challenges to peanut ($n = 50$; pass rate, 74%) and egg ($n = 50$; pass rate, 88%) were the most common, closely followed by the number of challenges to milk ($n = 36$; pass rate, 78%) and tree nuts ($n = 32$; pass rate, 81%). Tree nuts challenged included almond ($n = 19$), hazelnut ($n = 4$), walnut ($n = 4$), pecan ($n = 3$), and cashew ($n = 2$). Reprovocations were included for 6 children. The time between reprovocations ranged from 7 months to 3 years. No late-phase reactions were documented. The sIgE levels in the overall study ranged from 0.1 to 55.7 kU_A/L (median, 0.7 kU_A/L). The tIgE levels ranged from 2.2 to 5000 kU/L (median, 144.0 kU/L). The Ratio ranged from 0.1% to 10.5% (median, 0.6%).

Correlation between the Ratio and the outcome of challenge

The median Ratios for participants who passed or failed their oral food challenges to each of the allergen specificities are presented in Figure 1 and Table I. For oral food challenges to all food allergens, the median Ratio for participants who failed their oral food challenge was 1.48%, which was higher than the 0.49% Ratio for those who passed their oral challenge. There was an overall 25% decrease in odds of passing a food challenge for each unit increase in the Ratio (odds ratio [OR] 0.75 [95% CI, 0.58-0.95]; $P = .02$).

For challenges to less persistent food allergens, the median Ratio for participants who failed their challenge was not higher than the Ratio for those who passed their challenge (Figure 1, Table I). For challenges to these food allergens, there was no significant change in odds of passing a challenge for each unit increase in the Ratio (OR 1.02 [95% CI, 0.75-1.39]; $P = .89$). In fact, the median Ratio for egg challenges was lower for those who failed their challenge when compared with those who passed their challenge. Individual trends for milk, egg, wheat, and soy were similarly insignificant (data not presented).

In contrast, for challenges to more persistent food allergens, the median Ratio for participants who failed their challenge was 2.18%, which was higher than the 0.41% Ratio for those who passed their challenge (Figure 1, Table I). For challenges to these food allergens, there was a 40% decrease in odds of passing a food challenge for each unit increase in the Ratio (OR 0.60 [95% CI, 0.40-0.91]; $P = .02$). This trend was independently observed for peanut and tree nut challenges as well (Table I). Performance characteristics (ie, sensitivity, specificity, positive predictive value, negative predictive value) of various potential decision points for the Ratio are presented in Table II.

Predictive value of the Ratio versus sIgE alone

Receiver operator characteristic curves for the Ratio compared with sIgE alone are displayed in Figure 2. For challenges to all food allergens, the area under the curve (AUC) that represents the Ratio was significantly larger than that of sIgE alone (0.69 vs 0.55; $P = .03$). For challenges to less persistent food allergens, the AUC was not statistically different between the Ratio and sIgE alone (0.53 vs 0.57). Individual graphs for milk, egg, wheat, and soy were similarly insignificant (data not presented). In contrast, for challenges to more persistent food allergens, the AUC that represents the Ratio was significantly larger than that of sIgE alone (0.81 vs 0.54; $P < .01$). This trend also was individually observed for oral challenges to peanut (0.78 vs 0.56; $P = .08$) and tree nuts (0.85 vs 0.60; $P = .14$).

DISCUSSION

In the current study, the Ratio, also referred to as the IgE specific activity, was significantly correlated with the outcome of oral food challenges to more persistent food allergens (ie, peanut, tree nuts, shellfish, seeds), especially to peanut and tree nuts. For these allergens, a lower Ratio correlated with an increased probability of passing the challenge to confirm the development of tolerance. Furthermore, the Ratio was significantly more accurate than sIgE alone in predicting the outcome of challenges performed to confirm the development of tolerance to these food allergens. However, there were no significant correlations for less persistent food allergens (ie, milk, egg, wheat, soy).

Our findings for less persistent food allergens (ie, milk, egg, wheat, soy) are consistent with previous literature. Consistent with Mehl et al,⁷ the Ratio is not more accurate than sIgE alone in predicting the challenge outcome to these allergens. The current study data expand the literature by including more persistent food allergens (ie, peanut, tree nuts, shellfish, seeds). This first glimpse into the correlation between the Ratio and tolerance to these more persistent allergens showed a statistical significance, in which a lower Ratio correlates with an increased probability of tolerating the allergen and passing the challenge. More importantly, we found that the Ratio is significantly more accurate than sIgE alone in predicting tolerance and passing the challenge to these more persistent food allergens, especially to peanut and tree nuts. With further research to determine optimal predictive cutoff points, our finding can potentially improve clinical practice decision points and change current clinical practice.

The differential relevance of the Ratio in findings between more persistent and less persistent food allergens may be related to several factors. Food allergies outgrown earlier in life may resolve before other atopic factors are acquired that may raise the tIgE level. Matricardi et al¹⁰ observed a direct relationship between increasing sIgE and tIgE levels with age in children with atopy as well as an association with acquired respiratory allergic disease after the age of 5 years. Increasing IgE values over time may be composed of nonspecific IgE and cross-reactive but clinically irrelevant allergen sIgE that may lead to false-positive IgE values for the specific food allergen in question. These trends also may reflect the difference in sIgE analysis of food allergens whose risks are outgrown and those whose risks are not outgrown. For example, higher diagnostic decision point IgE values for soy and wheat³ may increase chances of false-positive IgE values or raise the predictive Ratio. A clinical confounding factor is that challenges may not have been performed for younger infants and children due to clinician or parental concerns for safety. This may explain why results for less persistent food allergens (ie, milk, egg, wheat, and soy) did not show a trend. These children may have avoided suspect food allergens longer with false-positive skin prick test or serum IgE results in scenarios that may not have been convincing for IgE-mediated anaphylaxis. Further subanalysis of children challenged with extensively heated milk or egg versus other milk or egg preparations could be clinically useful for the sIgE (including casein and ovomucoid) and the Ratio challenge decision points.

Four IgE humoral immune response parameters have been shown to alter mast cell and basophil mediator release in the patient with allergy.¹¹ These are the IgE antibody concentration, affinity (tightness of binding), clonality (epitope specificity), and IgE specific activity (the Ratio). These 4 humoral immune response parameters are operationally important in translating a

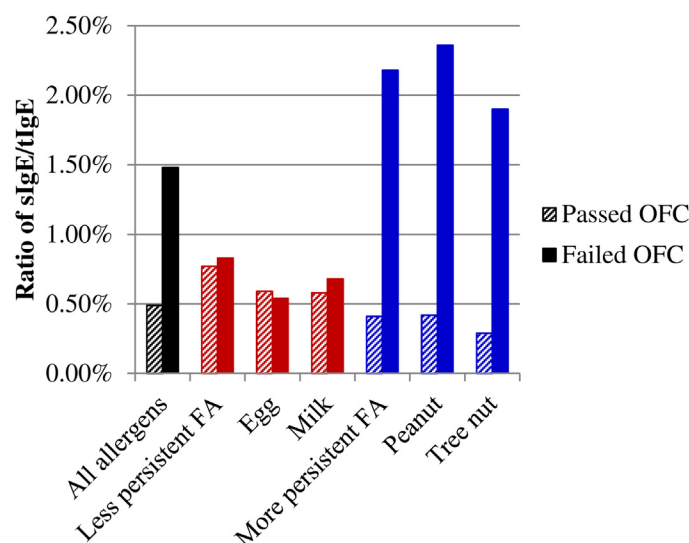


FIGURE 1. Median Ratio stratified by outcome of oral food challenge. “Less persistent FA” refers to milk, egg, wheat, and soy as a group (red); “more persistent FA” refers to peanut, tree nuts, shellfish, and seeds as a group (blue). Overall, the Ratio for participants who failed their OFC was higher than the Ratio for those who passed, especially for more persistent allergens (eg, peanut and tree nuts). OFC, Oral food challenge.

TABLE I. Correlation between the median Ratio and the outcome of oral food challenge

	Ratio, %	
	Passed OFC (n = 158)	Failed OFC (n = 37)
All allergens (n = 195)	0.49	1.48
Milk, egg, wheat, and soy (n = 102)	0.77	0.83
Egg (n = 50)	0.59	0.54
Milk (n = 36)	0.58	0.68
Peanut, tree nuts, shellfish, and seeds (n = 93)	0.41	2.18
Peanut (n = 50)	0.42	2.36
Tree nut (n = 32)	0.29	1.90

OFC, Oral food challenge.

state of sensitization (IgE antibody positivity) into a state of clinically manifested allergic symptoms. The diagnostic and clinical importance of the Ratio is less intuitive than the IgE antibody concentration, affinity, and specificity. Federly et al¹² observed correlations between tIgE and sIgE to egg, milk, peanut, and soy, with further clarification warranted for clinical outcome correlation. Our proposed mechanism that underlies the utility of the Ratio is that the higher the Ratio of a particular IgE antibody specificity, the higher the probability that there is a sufficient surface density of IgE antibody molecules on mast cells and basophils of the same allergen specificity to induce mediator release after an allergen encounter. The Ratio more accurately reflects specific binding capacity on the surface of mast cells and basophils, and thus the probability of allergen cross-linking and subsequent activation. This reduces the false-positive test rate that may be associated with nonassociated IgE and confounding immune markers not represented on testing.

Although allergen avoidance currently remains the primary course of action for patients with food allergy,¹³ unintentional exposure is not uncommon. Due to the potentially life-threatening

TABLE II. Performance characteristics of various potential decision points for the Ratio

	Potential decision points for the Ratio					
	0.5%	1.0%	1.5%	2.0%	2.5%	3.0%
Sensitivity (%)	68	62	49	43	27	22
Specificity (%)	56	69	78	84	87	92
Positive predictive value (%)	26	32	34	38	33	40
Negative predictive value (%)	91	89	87	86	84	83

nature of food allergy, constant vigilance is required by parents to ensure that their child avoids exposure to food allergens. Given the ubiquity of food, absence of a cure, and limited treatment options, food allergy has a profound psychological and social impact on the daily lives of affected children and their families, which impairs quality of life, straining relationships, and limiting social interaction.¹⁴⁻¹⁷ Parental burden can result from anxiety related to perceived severity of the allergy, loss of control of the environment, and fear that certain food allergies may not be outgrown.¹⁴ Children themselves may also experience significant stress and anxiety as a result of their food allergies and often face bullying in school.¹⁸⁻²⁰ In addition, children may experience nutritional deficiencies due to strict food allergen avoidance measures. A recent study found that children with milk allergy or with multiple allergies were smaller and had lower weight and body mass index, which indicates growth impairment.²¹ Avoidance of peanuts, tree nuts, and seeds also may place strain on families who choose to avoid other protein sources such as meat for religious or health reasons. Gaining tools to improve predictability of a child passing his or her oral food challenge to confirm the development of tolerance as early as possible will lessen the burden of the allergy on the child and family.

Allergists are often reluctant to perform open oral challenges to confirm the development of tolerance for peanuts, tree nuts, shellfish, and seeds because these food allergens are associated

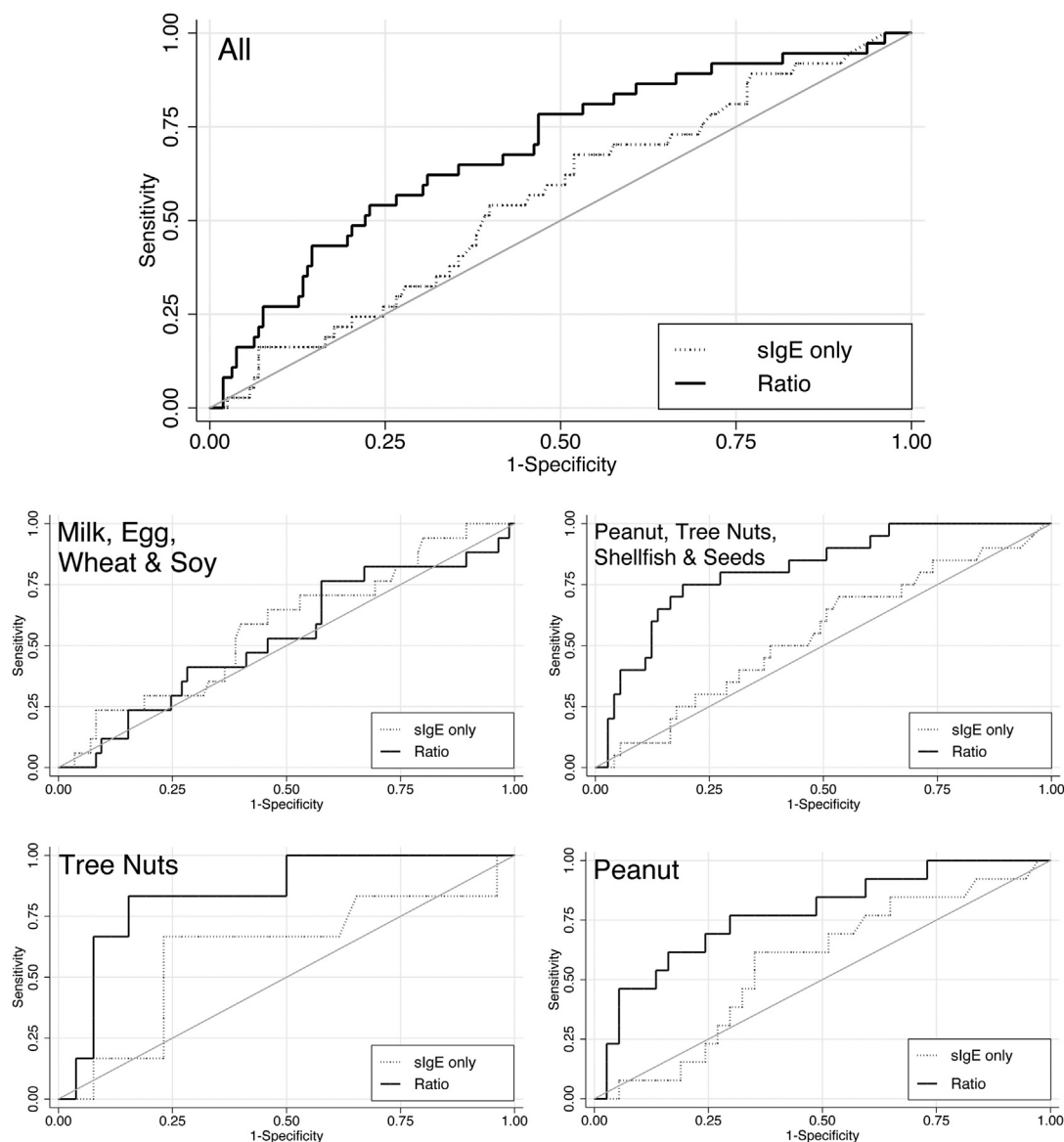


FIGURE 2. Receiver operator characteristic (ROC) curves for the Ratio compared with sIgE alone. A larger ROC AUC indicates that the test is more accurate in predicting the outcome of challenges performed to confirm the development of tolerance to the food. Overall, the AUC that represents the Ratio (*solid line*) was significantly larger than that of sIgE alone (*dotted line*), especially for more persistent allergens such as peanut and tree nuts.

with a persistent risk of anaphylaxis. Most allergists are not directly affiliated with a medical center or may practice in more rural areas, which makes transfer to an emergency center for treatment of anaphylaxis more time consuming. We provide evidence for a potentially more accurate diagnostic marker that involves the Ratio for these food allergens. Our theory is that the Ratio may be superior to sIgE levels alone to predict outcome of challenges, performed to confirm the development of tolerance, because it takes into account the raised IgE levels that are due to other IgE-mediated atopic conditions rather than the targeted food allergen. This gives physicians an additional risk parameter to consider when evaluating patients for readiness to proceed with a challenge to confirm the development of tolerance. Use of the Ratio along with established skin prick testing decision points

may encourage allergists to proceed with oral challenges for these food allergens to which development of tolerance is considered unusual and unlikely. Enabling allergists to offer open oral food challenges safely at younger ages and higher sIgE levels will diminish the impact that food allergy has on their patients' overall quality of life.

Several limitations to this study should be highlighted. First of all, retrospective studies have many limitations. Use of medical records assumed their accuracy and completeness, which may not always be the case. Although the oral food challenges performed were not blinded or placebo controlled, open office challenges are more commonly used by allergists in the outpatient setting. Furthermore, our small sample size, limited to one allergy outpatient clinic, may limit generalizability of findings to other populations.

In conclusion, our findings suggest that the Ratio is more accurate than sIgE alone in predicting outcomes of challenges performed to confirm the development of tolerance to select food allergens, especially to peanut and tree nuts. The Ratio may be a useful serologic indicator to identify patients most likely to pass an oral challenge to these food allergens.

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